

We claim:

1. A method for detecting the presence or amount of one or more biologically active natriuretic peptides of interest in a sample, comprising:

assaying said sample to provide an assay result related to the presence or amount of said biologically active natriuretic peptide(s) of interest in said sample, wherein said assay is performed under conditions selected to provide a detectable signal related to the presence or amount of a biologically active natriuretic peptide, and at least a 5-fold reduction in said signal from an equimolar amount of one or more biologically inactive peptides formed by cleavage of at least one peptide bond of said biologically active natriuretic peptide.

2. A method according to claim 1, wherein the biologically inactive natriuretic peptide is cleaved between cysteine residues forming an intramolecular disulfide bond *in vivo*.

3. A method according to claim 1, wherein the biologically active natriuretic peptide is BNP<sub>77-108</sub>, and wherein the biologically inactive peptide is selected from the group consisting of BNP<sub>94-108</sub>, BNP<sub>90-108</sub>, BNP<sub>81-108</sub>, BNP<sub>79-108</sub>, BNP<sub>79-106</sub>, and BNP<sub>77-106</sub>.

4. A method according to claim 1, wherein the biologically active natriuretic peptide is ANP<sub>99-126</sub>, and wherein the biologically inactive peptide is selected from the group consisting of ANP<sub>113-126</sub>, ANP<sub>105-126</sub>, ANP<sub>102-126</sub>, ANP<sub>99-124</sub>, and ANP<sub>102-124</sub>.

5. A method according to claim 1, wherein the sample is from a human.

6. A method according to claim 1, wherein the sample is selected from the group consisting of blood, serum, and plasma.

7. A method according to claim 1, wherein said assay is an immunoassay.

8. A method according to claim 7, wherein said immunoassay is formulated using one or more antibodies selected to bind to an epitope that is partially or completely lost in said biologically inactive natriuretic peptide as compared to said biologically active natriuretic peptide.

9. A method for detecting the presence or amount of one or more natriuretic peptides of interest in a sample, comprising:

assaying said sample to provide an assay result related to the presence or amount of said natriuretic peptide(s) of interest in said sample, wherein said assay is performed under conditions selected to provide a detectable signal related to the presence or amount of an intact natriuretic peptide, and at least a 5-fold reduction in said signal from an equimolar amount of a fragment formed by removal of a portion of the intact natriuretic peptide.

10. A method according to claim 9, wherein the biologically natriuretic peptide fragment is formed by cleavage of the intact natriuretic peptide between cysteine residues forming an intramolecular disulfide bond *in vivo*.

11. A method according to claim 9, wherein said assay does not appreciably detect an equimolar amount of said fragment formed by removal of an N-terminal portion of the intact natriuretic peptide.

12. A method according to claim 9, wherein the intact natriuretic peptide is BNP<sub>77-108</sub>, and wherein the fragment formed by removal of an N-terminal portion of the intact natriuretic peptide is selected from the group consisting of BNP<sub>94-108</sub>, BNP<sub>90-108</sub>, BNP<sub>81-108</sub>, BNP<sub>79-108</sub>, and BNP<sub>79-106</sub>.

13. A method according to claim 9, wherein the intact natriuretic peptide is ANP<sub>99-126</sub>, and wherein the fragment formed by removal of an N-terminal portion of the intact natriuretic peptide is selected from the group consisting of ANP<sub>113-126</sub>, ANP<sub>105-126</sub>, ANP<sub>102-126</sub>, and ANP<sub>102-124</sub>.

14. A method according to claim 9, wherein the sample is from a human.

15. A method according to claim 9, wherein the sample is selected from the group consisting of blood, serum, and plasma.

16. A method according to claim 9, wherein said assay is an immunoassay.

17. A method according to claim 16, wherein said immunoassay is formulated using one or more antibodies selected to bind to an epitope that is partially or completely lost upon removal of the N-terminal portion of the intact natriuretic peptide.

18. A method for detecting the presence or amount of one or more natriuretic peptides of interest in a sample, comprising:

assaying said sample to provide an assay result related to the presence or amount of said natriuretic peptide(s) of interest in said sample, wherein said assay result depends upon an antibody selected to specifically bind to a biologically active natriuretic peptide, wherein said specific binding is measured relative to a biologically inactive peptide formed by cleavage of at least one peptide bond of said biologically active natriuretic peptide.

19. A method according to claim 18, wherein the biologically active natriuretic peptide is BNP<sub>77-108</sub>, and wherein the biologically inactive peptide is selected from the group consisting of BNP<sub>94-108</sub>, BNP<sub>90-108</sub>, BNP<sub>81-108</sub>, BNP<sub>79-108</sub>, BNP<sub>79-106</sub>, and BNP<sub>77-106</sub>.

20. A method according to claim 18, wherein the biologically active natriuretic peptide is ANP<sub>99-126</sub>, and wherein the biologically inactive peptide is selected from the group consisting of ANP<sub>113-126</sub>, ANP<sub>105-126</sub>, ANP<sub>102-126</sub>, ANP<sub>99-124</sub>, and ANP<sub>102-124</sub>.

21. A method according to claim 18, wherein the sample is from a human.

22. A method according to claim 18, wherein the sample is selected from the group consisting of blood, serum, and plasma.

23. A method according to claim 1, wherein the method further comprises relating the presence or amount of said natriuretic peptide(s) of interest to the presence or absence of a disease or a prognosis associated with a disease.

24. A method according to claim 23, wherein the disease is stroke, congestive heart failure, cardiac ischemia, systemic hypertension, acute coronary syndrome, and acute myocardial infarction

25. A method according to claim 24, further comprising selecting a treatment regimen based on the presence or absence of a disease or a prognosis associated with a disease.
26. A method according to claim 9, wherein the method further comprises relating the presence or amount of said natriuretic peptide(s) of interest to the presence or absence of a disease or a prognosis associated with a disease.
27. A method according to claim 26, wherein the disease is stroke, congestive heart failure, cardiac ischemia, systemic hypertension, acute coronary syndrome, and acute myocardial infarction
28. A method according to claim 27, further comprising selecting a treatment regimen based on the presence or absence of a disease or a prognosis associated with a disease.
29. A method of inhibiting degradation of a natriuretic peptide present in a system comprising a prolyl-specific DPP, comprising:
- administering one or more inhibitors of prolyl-specific DPP in an amount sufficient to inhibit degradation of the natriuretic peptide.
30. A method according to claim 29, wherein the inhibitor(s) of prolyl-specific DPP comprise a dipeptide analogue comprising an aza, azetadine, boronate, hydroxylamine, or phosphonate moiety.
31. A method according to claim 29, wherein the inhibitor(s) of prolyl-specific DPP comprise an antibody or fragment thereof.
32. A method for increasing the level of natriuretic peptide function in a subject, comprising:
- administering one or more inhibitors of prolyl-specific DPP to said subject in an amount sufficient to inhibit degradation of the natriuretic peptide in said subject.
33. A method according to claim 32, wherein one or more additional molecules selected from the group consisting of inhibitors of neutral endopeptidase and natriuretic peptides are also administered to said subject.

34. A pharmaceutical composition comprising one or more inhibitors of prolyl-specific DPP and one or more additional molecules selected from the group consisting of inhibitors of neutral endopeptidase and natriuretic peptides.

35. A method of selecting an antibody for use in an assay, comprising:

selecting an antibody that provides a detectable signal related to the presence or amount of a biologically active natriuretic peptide, and to provide at least a 5-fold reduction in said signal from an equimolar amount of a biologically inactive peptide formed by cleavage of at least one peptide bond of said biologically active natriuretic peptide; or

selecting an antibody that specifically binds to a biologically active natriuretic peptide, wherein said specific binding is measured relative to a biologically inactive peptide formed by cleavage of at least one peptide bond of said biologically active natriuretic peptide; and

formulating said assay using said selected antibody.

36. A method according to claim 35, wherein the biologically active natriuretic peptide is BNP<sub>77-108</sub>, and wherein the biologically inactive peptide is selected from the group consisting of BNP<sub>94-108</sub>, BNP<sub>90-108</sub>, BNP<sub>81-108</sub>, BNP<sub>79-108</sub>, BNP<sub>79-106</sub>, and BNP<sub>77-106</sub>.

37. A method according to claim 35, wherein the biologically active natriuretic peptide is ANP<sub>99-126</sub>, and wherein the biologically inactive peptide is selected from the group consisting of ANP<sub>113-126</sub>, ANP<sub>105-126</sub>, ANP<sub>102-126</sub>, ANP<sub>99-124</sub>, and ANP<sub>102-124</sub>.

38. A method of selecting an antibody for use in an assay, comprising:

selecting an antibody that provides a detectable signal related to the presence or amount of an intact natriuretic peptide, and to provide at least a 5-fold reduction in said signal from an equimolar amount of a fragment formed by removal of a portion of the intact natriuretic peptide; or

selecting an antibody that specifically binds to an intact natriuretic peptide, wherein said specific binding is measured relative to a fragment formed by removal of a portion of the intact natriuretic peptide and

formulating said assay using said selected antibody.

39. A method according to claim 35, wherein the biologically active natriuretic peptide is BNP<sub>77-108</sub>, and wherein the biologically inactive peptide is selected from the group consisting of BNP<sub>94-108</sub>, BNP<sub>90-108</sub>, BNP<sub>81-108</sub>, BNP<sub>79-108</sub>, and BNP<sub>79-106</sub>.

40. A method according to claim 35, wherein the biologically active natriuretic peptide is ANP<sub>99-126</sub>, a and wherein the biologically inactive peptide is selected from the group consisting of ANP<sub>113-126</sub>, ANP<sub>105-126</sub>, ANP<sub>102-126</sub>, ANP<sub>99-124</sub>, and ANP<sub>102-124</sub>.

41. A method according to claim 35, wherein said antibody is selected from an antibody expression library.

42. A method according to claim 38, wherein said antibody is selected from an antibody expression library.